REMARKS

I. Status of the claims

Claims 1-4, 7-16, 20-27, and 30-44 are pending. Claims 39-44 remain withdrawn and claims 5, 6, 17-19, 28, and 29 remain cancelled. Claims 1, 16, and 27 have been amended to more clearly recite the claimed invention, as based upon the supporting specification; claims 9, 21, and 32 have been amended to make their respective recitations consistent with the independent claims; and claims 16, 20, and 21 have been amended to specify that the instructions are computer-executable instructions. No new matter has been added through these amendments.

II. Rejection under 35 U.S.C. § 101

The examiner has rejected claims 16 and 20-26 under 35 U.S.C. § 101 because the claimed invention is alleged directed to non-statutory subject matter.

The examiner states that the rejection would be overcome if the claims were amended to recite "computer-executable instructions." Applicants appreciate the examiner's comments. In this response, Applicants have amended claims 16, 20, and 21 based on the examiner's recommendations.

Accordingly, Applicants respectfully request that this rejection under 35 U.S.C. § 101 be withdrawn.

III. New Matter Rejection

The examiner has rejected claims 1-4, 7-16, 20-27, and 30-38 under 35 U.S.C. § 112, first paragraph as failing to comply with the written description requirement. The examiner states that this is a new matter rejection. In this response, Applicants have amended independent claims 1, 16, and 27 to more clearly show that the claimed invention does not contain any new matter.

The rejection relates to the coupling step and its support in paragraph 64. Paragraph 64 discloses, in part:

> [0064] The conjugate caps can then be coupled to form artificial molecular species whose interaction with the external molecule will be calculated to cancel out the artificial molecular interaction with individual caps. Thus the calculation of the original interaction energy between the molecule M and the protein P can

be replaced by calculation of interaction energy between molecule M and individual protein fragments. The two protein fragments whose interactions with the molecule need to be calculated are the capped protein fragments having the molecular formula

$$C^{i-1*}{}_{ap}A_iC^{i}{}_{ap} = NH_2R_iC_\alpha HCOHNR_{i+1}C_\alpha H_2$$

and the coupled caps having the molecular formula

$$C^{i*}{}_{ap}C^{i}{}_{ap} = NH_2R_{i+1}C_\alpha H_2$$

Since these fragments are relatively small molecules, the interaction energy between the M molecule and these small fragments can be calculated by *ab initio* methods with high efficiency. Since these individual interaction energies are calculated independent of each other, one can easily perform desired *ab initio* calculations on parallel or multi-processor computers to achieve greater real-time throughput.

Based on this disclosure, and in particular the portions emphasized above, Applicants recite the following coupling step: "coupling each pair of conjugate caps to form one or more coupled caps." As shown in paragraph 64, the conjugate caps are coupled to form artificial molecular species. The artificial molecular species are later referred to as coupled caps. Accordingly, Applicants respectfully submit that the limitation of coupling the conjugate caps to form coupled caps is supported by the specification.

Any small differences between the recited subject matter and that disclosed in pargraph 64 is acceptable under 35 U.S.C. § 112, first paragraph. As noted in the last response, it is well established in case law that an *in haec verba* recitation is not necessary to comply with the written description requirement. *See In re Smythe*, 178 USPQ 279 (CCPA 1973); *Lockwood v. American Airlines, Inc.*, 41 USPQ2d 1961 (Fed. Cir. 1997). Mere rephrasing of a passage does not constitute new matter. See MPEP § 2163.07.

In view of these additional amendments, Applicants respectfully request that the examiner withdraw the new matter rejection under 35 U.S.C. § 112, first paragraph.

IV. Written Description Rejection

The examiner has rejected claims 1-4, 7-16, 20-27, and 30-38 under 35 U.S.C. § 112, first paragraph as failing to comply with the written description requirement. The examiner states that the term "conjugate caps" is not sufficiently described in the specification such that one skilled in the art would be apprised of the structure intended. Applicants continue to traverse this rejection.

According to MPEP § 2163.04, a description as filed is presumed to be adequate, unless or until sufficient evidence or reasoning to the contrary has been presented by the examiner to rebut the presumption. *See In re Marzocchi*, 439 F.2d 220, 224 (CCPA 1971). The examiner has the initial burden of presenting by a preponderance of the evidence why a person skilled in the art would not recognize in an applicant's disclosure a description of the invention defined by the claims. *In re Wertheim*, 541 F.2d 257, 263 (CCPA 1976).

In this case, the examiner has not presented sufficient evidence or reasoning to rebut the presumption that the written description is adequate. The evidence that has been presented by the examiner, raising questions regarding different ways the term "conjugate caps" may be interpreted, certainly does not meet the preponderance-of-the-evidence standard required by the case law to satisfy this burden.

In the previous response, Applicants demonstrated how the conjugate caps work and directed the examiner to the sections of the specification supporting this feature of the invention. A further explanation showing how one skilled in the art would interpret the specification was provided by Applicants in the form of the Addendum was prepared by Dr. John Z. H. Zhang. Applicants have even offered the examiner an example on what the conjugate caps would be based on the tripeptide shown in Figure 1. Yet, despite this detailed showing, the examiner dwells on the "confusion" created by this term and the alleged inconsistencies at various points in the specification.

The analysis of whether the specification complies with the written description requirement calls for the examiner to compare the scope of the claim with the scope of the description to determine whether an applicant has demonstrated possession of the claimed invention. Such a review is conducted from the standpoint of one of skill in the art at the time the application was filed. *See Wang Labs. v. Toshiba Corp.*, 993 F.2d 858, 865 (Fed. Cir. 1993). After a thorough reading and evaluation of the content of the application, the examiner has the initial burden of presenting evidence or reason why a person skilled in the art would not recognize that the written description of the invention provides support for the claims. *In re Wertheim*, 541 F.2d 257, 262 (CCPA 1976).

Thus the focus of this analysis should lie on the *claimed invention* and whether Applicants have provided sufficient written description to support the *claims*. The examiner's analysis in this case, however, fails to analyze the claimed invention in any detail. If analyzed

properly, it will be clear that Applicants have disclose the invention is sufficient detail to demonstrate possession of the claimed invention. The term "conjugated caps," as recited in the claims, does not present a concept so confusing and so cryptic that one skilled in the art could not understand what the term means in the context of the claims. This is especially true in view of Applicants' comments demonstrating how one skilled in the art would interpret these terms.

The correct test is whether Applicants have provided sufficient evidence to place one skilled in the art in possession of the claimed invention. This has clearly been satisfied. Without question, one skilled in the art would understand what Applicants are attempting to claim. As set forth above, the presumption is that the written description is adequate. The examiner has not shown through a preponderance of the evidence that this requirement has not been met. For these reasons, Applicants respectfully request that the examiner withdraw this rejection under 35 U.S.C. § 112, first paragraph.

Applicants provide, for the examiner's convenience, the following remarks regarding the conjugate caps, as set forth in the previous response:

Applicants direct the examiner's attention to paragraphs 40-42, which should be analyzed in view of the figures, particularly Figure 1. Figure 1 exemplifies a graphical representation of an extended tripeptide showing the locations of the decomposition points where conjugated caps are introduced. See paragraph 12. Paragraphs 40-41 discuss how one skilled in the art approaches the application of the caps to the tripeptide exemplified in Figure 1.

As discussed in paragraph 40, the first cap on the A2 molecular fragment in Figure 1, C^1_{ap}, should represent the electronic effect of everything to the right side of the first decomposition point. Looking at Figure 1, the first decomposition point occurs between the nitrogen atom of the nA1 fragment that is bonded to the carbon atom of the A2 fragment. Everything to the right side of the first decomposition points in Figure 1 is represented as $C_\alpha H(R_2)CONHC_\alpha H(R_3)COO^-$. One skilled in the art could therefore choose $C_\alpha H(R_2)CONH_2$ as a cap to mimic the functionality present in the larger molecule fragment. In this scenario, C^1_{ap} is thus $C_\alpha H(R_2)CONH_2$.

As further discussed in paragraph 40, C^{1*}_{ap}, the conjugate cap to C^1_{ap}, should closely represent the electronic effect of nA1 on the A2 unit; in other words, everything to the left of the first decomposition point. nA1 is represented in Figure 1 as $H_3N^+C_\alpha H(R_1)CONH$. One skilled

in the art could therefore choose NH_2 (NH_3^+) to mimic the amine functionality present in the larger molecular fragment. (Protons can be removed or added to the caps, as appreciated by those of skill in the art, to represent the caps in either a charged state or a neutral state.) Thus, in this scenario, C^{1*}_{ap} is NH_2. Alternatively, one skilled in the art could choose a larger cap such as $C_\alpha H_2(R_1)CONH$ to capture the amide functionality of the molecular fragment. However, for the purposes of this explanation, C^{1*}_{ap} will represent NH_2.

As discussed in paragraph 42, after a molecule has been decomposed and capped with conjugate caps to create a plurality of molecular portions, the molecular portions may be used to measure intermolecular interaction energy. In the example discussed above, there are two molecular portions: the nA1 molecular fragment that has been capped with $C_\alpha H(R_2)CONH_2$, i.e. $H_3N^+C_\alpha H(R_1)CONH\ C_\alpha H(R_2)CONH_2$, and the molecular fragment consisting of A2 and A3c that has been capped with NH_2, i.e. $H_2NC_\alpha H(R_2)NH\ C_\alpha H(R_3)COO^-$. The caps are coupled to form conjugated caps. In this case, the $C_\alpha H(R_2)CONH_2$ cap is coupled with the NH_2 cap to form $H_2N\ C_\alpha H(R_2)CONH_2$. See paragraph 64 for an additional discussion of the coupling process.

A second molecular is introduced, and the interaction energies are determined between each molecular portion ($H_3N^+C_\alpha H(R_1)CONH\ C_\alpha H(R_2)CONH_2$ and $H_2NC_\alpha H(R_2)NH\ C_\alpha H(R_3)COO^-$) and the second molecule, and between the conjugated caps ($H_2N\ C_\alpha H(R_2)CONH_2$) and the second molecule. Each cap of the conjugated caps is thus part of two interaction energy equations. When calculating an intermolecular interaction energy, the interaction energy of conjugated caps is discounted so that an accurate determination of the intermolecular interaction energy between two molecules can be determined. This allows for a skilled artisan to choose various caps, provided the cap reasonably mimics the molecular fragment that it is substituted for. It does not matter if different skilled artisans were to choose different caps, as the conjugate caps, regardless of which cap is used, will be accounted for in the total intermolecular interaction energy calculation.

As can be seen in the exemplified tripeptide shown in Figure 1 and discussed in paragraphs 40-42 of the specification, one skilled in the art would understand how conjugate caps are determined and the relationship the conjugate caps have with each other and to the first molecule in the context of determining the total intermolecular interaction energy.

Applicants provide the above-described model as a simple example using a molecule that contains one decomposition point. As shown in Figure 1, the peptide could contain two (or

more) decomposition points. For molecules containing additional decomposition points, a skilled artisan would simply apply the process discussed above to each molecular fragment.

Another example of how the conjugate caps may be added to a molecule is provided in the Addendum, provided in the previous response. The Addendum was prepared by Dr. John Z. H. Zhang, lead inventor on this application and Professor of Chemistry at New York University. The Addendum illustrates another example of how a molecule can be decomposed into molecular fragments, the capping of the molecule with a small molecular species (a cap), and the coupling of caps to form conjugate caps.

V. Conclusion

Except for issue fees payable under 37 C.F.R. §1.18, the Commissioner is hereby authorized by this paper to charge any additional fees during the entire pendency of this application including fees due under 37 C.F.R. §§1.16 and 1.17 which may be required, including any required extension of time fees, or credit any overpayment to Deposit Account No. 19-2380. This paragraph is intended to be a **CONSTRUCTIVE PETITION FOR EXTENSION OF TIME** in accordance with 37 C.F.R. §1.136(a)(3).

Respectfully submitted,

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Dated: December 30, 2008

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